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CONSENSUS STATEMENT

Determinants, consequences and potential solutions to poor adherence to anti-osteoporosis treatment: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF)

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Abstract

Summary Many patients at increased risk of fractures do not take their medication appropriately, resulting in a substantial decrease in the benefits of drug therapy. Improving medication adherence is urgently needed but remains laborious, given the numerous and multidimensional reasons for non-adherence, suggesting the need for measurement-guided, multifactorial and individualized solutions.

Introduction Poor adherence to medications is a major challenge in the treatment of osteoporosis. This paper aimed to provide an overview of the consequences, determinants and potential solutions to poor adherence and persistence to osteoporosis medication.

Methods A working group was organized by the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal diseases (ESCEO) to review consequences, determinants and potential solutions to adherence and to make recommendations for practice and further research. A systematic literature review and a face-to-face experts meeting were undertaken.

Results Medication non-adherence is associated with increased risk of fractures, leading to a substantial decrease in the clinical and economic benefits of drug therapy. Reasons for non-adherence are numerous and multidimensional for each patient, depending on the interplay of multiple factors, suggesting the need for multifactorial and individualized solutions. Few interventions have been shown to improve adherence or persistence to osteoporosis treatment. Promising actions include patient education with counselling, adherence monitoring with feedback and dose simplification including flexible dosing regimen. Recommendations for practice and further research were also provided. To adequately manage adherence, it is important to (1) understand the problem (initiation, implementation and/or persistence), (2) to measure adherence and (3) to identify the reason of non-adherence and fix it.

Conclusion These recommendations are intended for clinicians to manage adherence of their patients and to researchers and policy makers to design, facilitate and appropriately use adherence interventions.

Keywords Adherence · Determinants · Osteoporosis · Persistence · Solutions

Introduction

Poor or non-adherence to medication remains a major problem in most chronic diseases, including osteoporosis. Effective and safe medications are available to reduce the risk of fractures [1], but numerous patients do not initiate treatment for osteoporosis or do not take it appropriately, resulting in a substantial clinical and economic burden [2]. Initiation of

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osteoporosis therapy is even poorer than in other disease areas, with a substantial decrease in bisphosphonates initiation observed in the last few years in Europe and the USA [3, 4]. Investing in medication adherence could improve health outcomes and health system efficiency [5].

Poor or non-adherence with osteoporosis medications is not a new problem. Several studies have already assessed the consequences and burden of non-adherence with osteoporosis medications being one of the major challenges of successful osteoporosis management [6] and have highlighted the urgency of managing medication adherence. In 2012, a systematic review of interventions to improve adherence to osteoporosis medications suggested few high-quality studies and mixed effects of interventions [7]. In recent years, osteoporosis management has evolved (e.g. new treatments, new diagnostic tools, FLS organizations), more interventions to improve adherence have been tested and a better understanding of the determinants of non-adherence is available.

Considering the burden of non-adherence with osteoporosis medications and the need to provide up-to-date recommendations to manage medication adherence, a working group was convened by the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) to review the consequences and determinants of poor adherence and interventions to manage adherence and improve persistence to osteoporosis medication. In addition, this paper aims to provide recommendations for practice and for further research. Information included in this review could be of value to help not only clinicians to manage adherence of their patients but also for researchers and policy makers involved in osteoporosis.

Methods

An international working group was formed to review the consequences and determinants of poor adherence and interventions, to manage adherence and improve persistence to osteoporosis medication and to provide recommendations for practice and for further research. The working group comprised clinical scientists, researchers (including experts in adherence) and a patient selected by the Scientific Advisory Board of ESCEO.

In preparation for a working group meeting, a systematic literature review was conducted to identify articles about the determinants and interventions to improve adherence or persistence to osteoporosis medications. The literature search was conducted for articles up to December 2018 in PubMed. Further details about the search strategy and inclusion of articles can be found in Cornelissen et al. [8]

A face-to-face meeting then took place on 22 January 2019. The meeting started with three short presentations about the clinical and economic consequences of non-adherence to osteoporosis medications (JYR), the determinants of non-adherence to osteoporosis medications (MH) and the potential solutions to improve adherence to anti-osteoporosis medications (DC). A group discussion led by MH and ADP followed. Each participant had the opportunity to comment on the determinants, consequences and potential solutions and then to provide recommendations for practice and further research. Following this meeting and a symposium that was held at the World Congress of Osteoporosis (WCO-IOF-ESCEO congress, 6 April 2019), members of the writing team (MH, DC, BV, BA, JYR, JK, AG, PH) reviewed a first version of the article drafted by MH; this was then reviewed and commented on by all members of the working group.

Terminology

In the literature, a number of terms such as ‘adherence’, ‘compliance’, ‘concordance’ and ‘persistence’ have been used to define how patients take their medicines [9]. In 2012, a collaboration of European research groups in the field of medication adherence funded by the European Commission suggested the ABC taxonomy for describing and defining adherence to medications [9], which will be used in this paper. Adherence to medication is defined as ‘the process by which patients take their medications as prescribed, composed of A) initiation, B) implementation and C) discontinuation’ [9, 10]. *Initiation* occurs when the patient takes the first dose of a prescribed medication, *discontinuation* when the patient stops taking the medication and *implementation* is the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. Medication persistence is further defined as the length of time between initiation and the last dose, which immediately precedes discontinuation [9]. Overall, this definition is in agreement with the definition of the *Group for the Respect of Ethics Excellence in Science* in osteoporosis [11], with the exception that implementation has replaced compliance, and initiation is preferred over primary adherence.

Adherence to osteoporosis medications, clinical and economic consequences

In a recent review including 124 studies, the prevalence of medication adherence ranged from 12.9 to 95.4% [12]. Several studies have reported that initiation, implementation and persistence to osteoporosis medications are suboptimal. In line with treatment initiation rates in other diseases [13], about 20–30% of patients do not initiate a treatment after a prescription for oral bisphosphonates [14]. In addition, patients on bisphosphonates frequently miss doses and therefore do not implement as prescribed [15]. Persistence rates at 1 year for

oral bisphosphonates are commonly estimated between 16 and 60% [16–18], in line with a review of 95 clinical studies from different disease areas suggesting that about 40% of patients discontinued at 1 year [19]. For example, in a large observational Belgian study, persistence rates to oral bisphosphonates were estimated at 39.5% at 1 year, without a gap of more of 5 weeks in treatment [20], while only 48% of patients were adherent (defined as a medical possession ratio (MPR) ≥ 80%). In another study, van Boven et al. showed that persistence to weekly oral bisphosphonates was about 60% at 1 year and decreased to 25% at 5 years [21], in line with a Danish study [22]. Other studies have even reported that less than 20% were still on treatment as soon as after 12 months after treatment initiation [23]. Differences in methodologies (e.g. permissible gap to define persistence, adherence measures, incorporation of switchers) could explain the differences between studies and made direct comparison between them difficult.

Further, osteoporosis remains largely underdiagnosed and a substantial number of patients at increased risk of fractures do not even receive any prescription for osteoporotic therapy [24] or only calcium and vitamin D supplementation. The osteoporosis treatment gap was estimated between 25 and 95% in European countries [25]. Even in randomised controlled trials, persistence and adherence with therapy decline over time, and any reduced effectiveness caused by suboptimal adherence is to some extent already captured in clinical trials.

Different profiles of non-adherent patients could be identified [26]. Some patients never initiate a treatment, while others delay initiation of therapy. There are patients who frequently miss doses, and multiweek drug holiday periods have also been observed. Several patients further discontinue treatment earlier than prescribed. In a USA study, it was also observed that among discontinuers, about 45% [27] reinitiated therapy, with the majority doing so within 6 months of discontinuation, suggesting that many patients are thus exposed to multiple episodes of starting and stopping of drug actions. Finally, several medication switchers have been reported [28]. Failure to take account of switchers could distort estimates of adherence and persistence.

Poor persistence and adherence to osteoporosis medications reduce the potential benefits of osteoporosis therapy, lowering gains in bone mineral density and resulting in increased risk of fragility fractures [29]. Two systematic reviews and meta-analyses assessed the impact of adherence/persistence to oral bisphosphonates on fracture risk. The meta-analysis of Ross et al. [30] indicated that fracture risk increased by approximately 30% with non-adherence (defined as medical possession ratio < 80%) and by 30 to 40% with non-persistence. Similarly, Imaz et al. [31] reported that low adherence to oral bisphosphonates was significantly associated with increased non-vertebral fracture risk (relative risk (RR) of 1.16), increased hip fracture risk (RR 1.28) and increased vertebral fracture risk (RR 1.43).

Studies reporting adherence to osteoporosis medication and its relationship with fracture risk mainly focused on oral bisphosphonates, although data for other medications (e.g. teriparatide, raloxifene, denosumab or zoledronic acid) also revealed suboptimal levels [32, 33]. In a large US study, persistence to teriparatide and denosumab at 1 year were estimated at 69% and 58% [34]. Non-persistence to denosumab could further lead to important health problems as discontinuation with denosumab has recently been shown to be associated with rapid bone loss and increased risk of multiple vertebral fractures [35]. Persistence to yearly intravenous injection of zoledronic acid is also not convincing, as suggested by a study that showed that only one-third of patients agreed to a second administration after 1 year [36]. Furthermore, for some osteoporosis medications, persistence to generic formulations has been shown to be poorer than for branded formulations [37, 38].

A few model-based studies have estimated the economic consequences of non-adherence at a population level [2, 39–42], suggesting important clinical and/or economic implications of poor adherence/persistence with osteoporosis medications. For example, poor adherence with osteoporosis medications resulted in about 50% reduction in the potential benefits observed in clinical trials (in terms of fractures prevented and quality-adjusted life-years (QALY)) and a substantial deterioration of the cost-effectiveness resulting from these medications [2, 40]. Medication adherence has further become an important factor for inclusion in cost-effectiveness analyses in osteoporosis [43–45]. Interestingly, economic studies have also suggested that interventions to improve adherence may likely confer cost-effectiveness benefits [43]. Improving adherence to medication could lead to greater benefits that designing a new more effective drug [46].

Determinants of non-adherence

Adherence is a complex multidimensional phenomenon determined by the interplay of several factors. Numerous determinants of non-adherence have been identified in the literature [12, 47]. The World Health Organization has classified these factors into five main categories, i.e. patient-related, therapy-related, condition-related, health system and socio-economic factors [5]. Recently, Yeam et al. [12] conducted a systematic literature review up to January 2018 to review and identify factors that influence patients' adherence to anti-osteoporotic therapy. A total of 24 factors and 139 subfactors were identified from 124 relevant studies. The authors presented types and number of studies that presented the case for and against each specific factor and revealed that patient-related factors

were the most commonly studied category followed by therapy-related and condition-related category.

Condition-related factors that were associated with poorer medication adherence included polypharmacy and having gastro-intestinal diseases. History of falls, fractures and screening for osteoporosis were however not associated with higher adherence. This is important as patients with a recent fracture are at imminent risk of a further fracture [48]. *Patient-related factors* associated with poorer medication adherence included male gender, lower education levels, misconceptions about osteoporosis and lack of perceived benefits of therapy, whereas higher age was associated with higher medication adherence but only in half of the studies. Among *therapy-related factors*, medication side effects, complex instructions for medication administration and complex medication regimens were associated with poorer adherence and lower dosing frequency with higher adherence, while a history of anti-osteoporosis treatment was not found to be a predictor of adherence. *Health system-based factors* associated with poorer medication adherence included care under different medical specialties and lack of patient education (information sharing, counselling from healthcare professional, etc.). *Socio-economic-related factors* associated with poorer medication adherence included current smoking, lower income level and lack of medical insurance coverage [12].

This review did not classify the factors according to adherence level, i.e. initiation, implementation and persistence. In another review of systematic reviews that covered 19 disease areas [47], a total of 771 individual factors of medication adherence were identified of which most were determinants of implementation, and only 47 determinants of persistence with medication and no determinant were specifically provided for initiation. In the field of osteoporosis, the patient perceived need for treatment, patient knowledge, bone density testing, improved patient-provider relationship, hospitalizations and prescription use have been shown to be positively associated with initiating osteoporotic therapy [49–52]. Reasons for not initiating osteoporotic therapy also include lack of motivation, concern about side effects and medication costs [52]. Reasons for poor implementation and persistence with osteoporosis therapy include side effects of treatment, difficulties with medication intake (e.g. 30 min before breakfast), inconvenient dosing regimen, concern about treatment, no perceived benefits, drug cost, misinformation, insufficient motivation or dissatisfaction with their doctor visits [47, 53–55]. Adherence to osteoporosis medications is simply a matter of patient choice, and is due mostly to deliberative choice [56]. However, reasons for non-adherence can also be unintentional, resulting from forgetfulness, especially in holiday period [53], and some irrational behaviour could also be reported. Factors involved in treatment initiation may further differ than factors involved in persistence or implementation. As example, polypharmacy has been shown to have a positive effect on treatment initiation with patients who have not previously taken medication being less likely to start [14] while persistence and implementation are generally lower in patients on multiple medications [12]. Lau et al. conducted focus groups in Canada to understand reasons for non-adherence and included different patients' quotes regarding belief in the importance of taking medications for osteoporosis, medication-specific factors, beliefs regarding medications and health, relationships with healthcare providers and information exchange [57].

The patient participating at our working group stressed the importance of giving a positive message to the patient and not exaggerating the consequences if the patient does not take the drug. Web and social media nowadays also attract a lot of attention and could further negatively influence adherence to treatment.

Reasons for non-adherence are therefore numerous and multidimensional for the same patient. Each patient's reason(s) for non-adherence is different, depending on the interplay of these multiple factors, and could also change over time and be different for each key element of adherence. Medication adherence is therefore not predictable, suggesting the need for individualized solutions.

Review of interventions

In 2012, Hiligsmann et al. [7] reviewed and critically appraised interventions to improve adherence and persistence to osteoporosis medications. A total of 20 studies tested a patient adherence intervention and reported quantitative results on adherence. Education programs (e.g. written materials, counselling, motivational interviewing, combination) were the most frequent intervention ($n = 9$). Although patient education improved medication adherence in four studies, two large-scale randomized studies reported no benefits [58, 59]. Monitoring/supervision by bone mineral density or bone turnover markers were not shown to be associated with improved adherence. However, a positive message revealing a good bone turnover marker response was associated with a significant improvement in persistence [60]. Simplification of dosing regimens (with and without patient support program), electronic prescription and a pharmacist intervention was associated with improved adherence but only in couple of studies.

For the purpose of this working group, the previous systematic review was updated. A description of the literature search, data and critical appraisal can be found in the article of Cornelissen et al. [8]. A total of 15 studies were identified between June 2012 and December 2018. Very few high-quality studies (such as RCTs) were identified, and interventions were mainly single component intervention. Interventions were classified as patient education and/or support ($n = 9$), monitoring and supervision ($n = 2$), flexible

dosing regimen and patient support ($n = 3$) and interdisciplinary collaboration ($n = 1$). In each subtype of interventions, mixed results on adherence/persistence were found where some studies were shown to be successful and others not (see next section). Interventions which include counselling with education and/or flexible dosing regimens seem to be most effective, as well as interventions aiming on testing and initiating medication.

Recommendations for practice

Many factors affect medication adherence. Single interventions could work but certainly not for all patients. There is not one single intervention to manage adherence. Some recommendations to improve adherence are made below.

It is of primary importance to emphasize the need for treatment adherence and to talk about adherence with patients. To adequately manage medication adherence, at least three stages are recommended:

1. *What is the adherence problem (initiation, implementation and/or persistence)?* It is key to identify the element(s) of non-adherence problem(s) that you want to address with the patient(s).
2. *How to measure adherence?* Different methods are available to measure the elements of medication adherence. Prescription refills and databases are appropriate methods to measure initiation and discontinuation of therapy [61] while electronic monitoring is the preferred method for implementation, although could be difficult to set up in real-life settings [61]. The use of self-reports or pill counts could be alternative methods.
3. *What is the reason and how to fix it?* Given the numerous potential factors for non-adherence, it is therefore important to understand the reason(s) for non-adherence for each patient and to find an adequate personalized solution.

These three steps are in line with the Six Sigma framework to manage medication adherence developed by Vrijens et al. [62]. This framework includes definition (robust taxonomy), measure (operational definition and performance), analysis (understand the cause), addressing the cause and implementing solutions and measurement-guided adherence management.

In addition to the updated systematic review of adherence interventions in osteoporosis, a comprehensive list of interventions is provided with evidence about their effectiveness including systematic reviews of adherence interventions in other diseases including depression, cardiovascular diseases and hypercholesterolaemia [63–65] (Table 1). Patient education and counselling, adherence monitoring with feedback and dose simplification including flexible dosing regimen were associated with higher adherence improvements. We however acknowledge that the efficacy of these actions is still largely unknown and current data could be controversial.

Patient education and counselling were shown to improve post-fracture care and treatment initiation, with more controversial results on medication adherence. As a prominent example for post-fracture care, the PREVOST trial suggested that repeated oral and written information about fragility fractures and osteoporosis management by a case manager increased treatment initiation (53% initiated post-fracture care in the intervention compared to 33% in the control) [66]. In another study [67], patient education and referral to endocrinologist by a nurse were shown to improve the initiation of calcium and vitamin D, although up to 50% of patients with osteoporosis did not complete follow-up visits and/or did not adhere to treatment recommendations for osteoporosis. Assigning a screening coordinator to identify, educate and follow up with fragility fracture patients and inform their physicians of the need to evaluate bone health was also shown to increase treatment initiation [68]. A systematic screening using FRAX® was also shown to increase use of, and adherence to anti-osteoporosis medications in the UK SCOOP Trial [69]. In addition, an osteoporosis school program (i.e. four classes of 8–12 participants over 4 weeks), peer-led community education and mentorship program or patient education program were associated with improved knowledge of osteoporosis and initiation of treatment [70]. In a large pragmatic randomized controlled trial, however, telephonic motivational interviewing intervention was not associated with significant improvements in medication adherence [59].

Adherence monitoring with feedback was also associated with improved adherence. Stuurman-Bieze et al. [71] showed that a proactive pharmaceutical care including counselling at baseline and at 2 weeks and an active monitoring and counselling every 3 months by pharmacists for patients who should have redeemed a new prescription leads to improved adherence. Ducomlombier et al. [72] further suggests that phone calls by medical secretaries every 2 months to motivate patients to maintain good adherence to the treatment and to detect any difficulties in adherence with the prescription using non-incriminating questions were associated with improved adherence.

Dose simplification including flexible dosing regimen was associated with improved adherence. Offering patients a medication with less strict administration instructions such as the use of gastro-resistant risedronate tablets that could be taken after breakfast was associated with improved persistence to treatment [73]. Longer dosing regimen (such as 6-month subcutaneous injection of denosumab or yearly intravenous injection of zoledronic acid) can also be interesting to improve adherence, although adherence levels have also been disappointed and far from optimal (see previously). Finally, a flexible dosing regimen (before breakfast; in-between meals; before bedtime) was also shown to be associated with improved

Table 1 Evidence about the effectiveness of adherence-enhancing interventions

Intervention subclass	OP studies	Other conditions*	Conclusion
Education and support			
Patient education program	4	4	Mixed evidence of effectiveness
Patient counselling	1	10	Strong evidence of effectiveness
Patient education combined with counselling	11	15	Strong evidence of effectiveness
Provision of educational material	2	5	No evidence of effectiveness
Monitoring supervision			
Non-adherence monitoring	1	2	Limited evidence of effectiveness
Adherence monitoring combined with counselling	5	10	Strong evidence of effectiveness
Drug regimen combined with counselling	1	1	Limited evidence of effectiveness
Reminders to take the medication	1	7	Strong evidence of effectiveness
Monitoring biomarkers	3	N/a	No evidence of effectiveness
Dose regimen adjustment and simplification			
Dose simplification including flexible dosing regimen	4	8	Strong evidence of effectiveness
Individual medication program	1	1	Limited evidence of effectiveness
Costs covered	N/a	1	Limited evidence of effectiveness
Other subclasses			
Combination of interventions mentioned above	3	2	Mixed evidence of effectiveness
Other interventions	4	9	Low evidence of effectiveness

N/a not applicable

*Restricted to depression, cardiovascular diseases and hypercholesterolaemia

persistence, although there was no statistical difference in terms of adherence [74].

Improving *patient interaction and shared decision-making* can also lead to improve treatment initiation and potentially improve adherence. Several guidelines and international groups recommend that shared decision-making be part of standard treatment. In shared decision-making, both parties share information: the clinician offers options and describes their risks and benefits, and the patient expresses his or her preferences and values [75]. Each participant is thus armed with a better understanding of the relevant factors and shares responsibility in the decision about how to proceed [75]. Decision aids emphasize shared decision-making and include several features to support individualized treatment discussions like those needed for fracture prevention. Decision aids for a range of conditions have been shown to decrease decisional conflict, increase knowledge and (when probabilities are included in the aid) improve the accuracy of risk perception [76]. Some decision aids aiming to facilitate shared decision-making in osteoporosis have been designed and shown to improve the quality of clinical decisions about bisphosphonate therapy and may have improved adherence [77–79].

Providing patients with good quality information about osteoporosis, their risk and treatment options is needed as a crucial step to increase the diagnosis and treatment of osteoporosis. The *doctor* is therefore a key actor to improve medication adherence. As an educator and a partner in making treatment decisions, the doctor should be familiar with the medical evidence, able to discuss complex medical information in a manner that is understood by the patient and appropriately consider the patient's expectations, beliefs and concerns [80, 81]. A doctor should thus facilitate interaction with the patient and him/her, understand the patient's needs and investigate the type of treatment appropriate for the patients (e.g. dosing regimen).

Recommendations for further research

Some areas where further research is needed were identified. First, it is important to improve our understanding on what osteoporotic patients want, need and prefer and to better understand how and why patients will (not) be adherent. It is particularly important to understand the root causes for each aspect of adherence, i.e. initiation, implementation and persistence. Qualitative research is the best way to understand patients' needs and reasons for non-adherence and should be a starting point for designing appropriate interventions. Stated preference methods could also be interesting to reveal patients' preferences and important treatment characteristics [82].

Second, register-based studies can be attractive to investigate the importance of different factors and identify the strongest and most prevalent risk factors for poor adherence as targets for intervention. Big (pharmaco-epidemiologic) data provide new opportunities to help understand the reasons of medication non-adherence and may also prove helpful in assessing the effects of new initiatives in the area.

Third, with a better understanding of patients' needs and non-adherence factors, it would then be possible to design interventions that fit patients' needs and wishes on a personalized manner. It is indeed recommended to develop complex, individualized and multifactorial interventions. There is not one single intervention to manage adherence. Involving patients in the preparation, development and assessment of these complex interventions would be crucial [83]. Further research is also warranted on patient involvement in medication adherence research and patient empowerment and its role in promoting adherence. Complex interventions would thus need to be tested in large scale randomized controlled trials.

Fourth, as the cost of an adherence intervention may be high, it would also be important to identify patients that will be receptive to interventions and spend our limited resources on those patients. We further need patient outcome tools to better understand the patient perspective and patient biases in decision-making concerning osteoporosis therapies [84].

In addition, web-based applications could play a crucial role in supporting patients to improve their adherence to medication. Further research focusing on digital adherence interventions is necessary to determine their value and ideal ways to improve osteoporosis medication adherence.

Other areas for further research include the need to adequately communicate about osteoporosis, fracture risk and osteoporosis treatment to patients; development of shared decision-making; assessment of adherence-management model (such as the three-stage model proposed previously); innovative methods for monitoring medication adherence; and policy/healthcare systems initiatives to support adherence interventions.

Conclusions

Osteoporosis represents a significant healthcare burden in European countries which, due to increasing life expectancies, is predicted to increase further in the future [24]. Despite the increasing burden and the availability of effective treatments in reducing the risk of fractures, most patients are not taking their medication appropriately or do not even start an osteoporosis medication. Improving treatment initiation and adherence to therapy is therefore urgently needed to leverage in full the benefits of drug therapy.

Poor and non-adherence with medication is common with a treatment gap estimated between and 95% in European countries [25] and about half of the patients discontinuing therapy within 1 year. Reasons for non-adherence are numerous, diverse and multidimensional, depending on the interplay of multiple factors and may be different for each key element of adherence. Few single interventions have been shown to improve adherence or persistence to osteoporosis treatment. Potentially, promising interventions include patient education with counselling, adherence monitoring with feedback and dose simplification including flexible dosing regimen. Recommendations for practice and further research were provided, suggesting the need to emphasize the importance of adherence to treatment and to talk about adherence with patients, and the need to implement sound measures of adherence so that the intervention can be individualized. These recommendations are intended for clinicians to manage adherence of their patients and to researchers and policy makers to design, facilitate and appropriately use adherence interventions and to advance research in the field.

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Compliance with ethical standards

Conflict of interest MLB has received honoraria from Amgen, Bruno Farmaceutici, Kyowa Kirin; academic grants and/or speaker from Abiogen, Alexion, Amgen, Bruno, Farmaceutici, Eli Lilly, Kyowa Kirin, MSD, NPS, Servier, Shire and SPA; and consulting fees from Alexion, Bruno Farmaceutici, Kyowa Kirin, Servier and Shire.

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RR has been speaker bureau or member of scientific advisory boards for Danone, Echolight, Effryx, Mylan, Nestlé, ObsEva, Pfizer, Radius Health, Sandoz and TEVA/Theramex.

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